

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

EXELIXIS, INC.,
Patent Owner.

Case IPR2025-00427
Patent 12,128,039

**PATENT OWNER'S
DISCRETIONARY DENIAL BRIEF**

TABLE OF CONTENTS

	Page
I. Introduction.....	1
II. Background.....	4
A. Cabozantinib (L)-Malate.....	4
B. The '039 Patent	5
III. The Board Should Exercise Its Discretion to Deny	
Institution of the Petition	7
A. The Board Should Not Spend Its Limited Resources on the Petition in	
Light of Ongoing Hatch-Waxman Litigation.....	8
1. The Hatch-Waxman Framework Was Carefully Designed to	
Adjudicate Such Challenges	9
a. Institution Would Upset the Careful Balance Established	
by Congress	11
2. The Same or Similar Arguments Were Litigated and Rejected	
by the District Court in the MSN Litigation	14
a. Ground I.....	15

b.	Ground II	18
3.	The Petition Relies Heavily on Expert Testimony to Fill Substantial Gaps in the Cited Patents and Printed Publications	19
4.	The Merits of Petitioner’s Unpatentability Theories Are Weak	23
B.	The Petition Should Be Denied Under 35 U.S.C. § 325(d)	25
1.	<i>Advanced Bionics</i> Prong 1: The Office Already Considered the Same or Substantially the Same Art and Arguments.....	26
a.	Ground I.....	27
i.	The Office Considered Brown in View of Kubo	27
ii.	The Office Considered “Known” Formulation Techniques.....	31
b.	Ground II	33
i.	The Office Considered Robinson’s Substance.....	33

ii.	The Office Considered the Substance of the Petition’s Obviousness Argument Over Brown and Robinson.....	34
2.	<i>Advanced Bionics</i> Prong 2: Petitioner Has Not Identified a Material Error by the Office	37
a.	<i>BD</i> Factor (c): Asserted Art Was Extensively Evaluated During Examination	37
b.	<i>BD</i> Factor (e): Petitioner Has Not Identified Any Examiner Error	38
c.	<i>BD</i> Factor (f): No Additional Evidence Warrants Reconsideration	40
IV.	Conclusion	42

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Actavis Laboratories FL, Inc. v. United States</i> , 131 F.4th 1345 (Fed. Cir. 2025)	11
<i>Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH</i> , IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020)	<i>passim</i>
<i>Andrx Pharmaceuticals, Inc. v. Biovail Corp.</i> , 276 F.3d 1368 (Fed. Cir. 2002)	2, 11
<i>Azurity Pharmaceuticals, Inc. v. Exelixis, Inc.</i> , IPR2025-00210, Paper 2 (P.T.A.B. Nov. 18, 2024).....	13
<i>Becton, Dickinson & Co. v. B. Braun Melsungen AG</i> , IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017)	26, 34
<i>Bowtech, Inc. v. MCP IP, LLC</i> , IPR2019-00382 Paper 12 (P.T.A.B. Aug. 6, 2019).....	30
<i>Exelixis, Inc. v. Azurity Pharmaceuticals, Inc.</i> , No. 25-478-RGA (D. Del.)	9
<i>Exelixis, Inc. v. MSN Laboratories Private Ltd.</i> , No. 22-228-RGA (D. Del.)	<i>passim</i>
<i>FTC v. Actavis, Inc.</i> , 570 U.S. 136 (2013).....	9, 11
<i>Mylan Laboratories Ltd. v. Janssen Pharmaceutica NV</i> , IPR2020-00440, Paper 17 (P.T.A.B. Sept. 16, 2020)	11
<i>NHK Spring Co. v. Intri-Plex Technologies, Inc.</i> , IPR2018-00752, Paper 8 (P.T.A.B. Sept. 12, 2018)	26

<i>Par Pharmaceutical, Inc. v. TWI Pharmaceuticals, Inc.</i> , 773 F.3d 1186 (Fed. Cir. 2014)	24
<i>Weatherford U.S., L.P. v. Enventure Global Technology, Inc.</i> , IPR2020-01661, Paper 19 (P.T.A.B. Apr. 15, 2021)	31
<i>Ziegmann v. Stephens</i> , IPR2015-01860, Paper 13 (P.T.A.B. Sept. 6, 2017)	38

Statutes

21 U.S.C. § 355	8, 9
21 U.S.C. § 355(b)(2)	9
21 U.S.C. § 355(b)(2)(A)	10
21 U.S.C. § 355(b)(3)(D)(ii)	10
21 U.S.C. § 355(c)(3)(C), (D)	10
35 U.S.C. § 271(e)(2)	10
35 U.S.C. § 311(b)	19
35 U.S.C. § 311(c)(1)	14
35 U.S.C. § 314(a)	1, 41
35 U.S.C. § 325(d)	1, 3, 25, 41
Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, codified at 21 U.S.C. §§ 355, 360cc, and 35 U.S.C. §§ 156, 271	<i>passim</i>

Other Authorities

Acting Director’s March 26, 2025, Memorandum Regarding Interim Processes for PTAB Workload Management	7, 19
--	-------

Carlos A. Garcia & Jonathan Stroud, <i>Ships in the Night</i> , 68 Am. U. L. Rev. 1111, 1170 (2019).....	12
Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019).....	7, 14
FDA, <i>Guidance for Industry Q3B(R2) Impurities in New Drug Products</i> (2006)	35-36, 40
USPTO, <i>FAQs for Interim Processes for PTAB Workload Management</i> (Apr. 25, 2025), https://www.uspto.gov/patents/ptab/faqs/interim-processes- workload- management?utm_campaign=subscriptioncenter&utm_content =&utm_medium=email&utm_name=&utm_source=govdeliver y&utm_term=	20

I. INTRODUCTION

The Board should exercise its discretion to deny institution of this IPR under 35 U.S.C. § 314(a) and/or 35 U.S.C. § 325(d), because this Petition would not be an efficient use of the Board’s limited resources. Denying institution is justified based on at least the following factors: the prior and concurrent adjudication of closely-related issues in Hatch-Waxman litigation; the extent of the Petition’s reliance on expert testimony; the weakness of the unpatentability challenge; and the consideration of closely-related issues by the Office during examination of the ’039 patent and its family members.

First, the patent at issue in the Petition, U.S. Patent No. 12,128,039 (the “’039 patent”), is the subject of multiple ongoing litigations (involving Petitioner and others) in the United States District Court for the District of Delaware in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, codified at 21 U.S.C. §§ 355, 360cc, and 35 U.S.C. §§ 156, 271 (“Hatch-Waxman Act”). Under the statutory framework established by Congress in the Hatch-Waxman Act, those litigations were initiated when Petitioner (and the others) chose to submit what are known as “paragraph IV” notices challenging the validity of the ’039 patent. Notably, the arguments

raised in the Petition are *identical* to obviousness arguments Petitioner has raised in its paragraph IV challenge—indeed, Petitioner “incorporates by reference” in its paragraph IV notice “the bases for invalidity as set forth in [the] petition[.]” Ex. 2018 (Annexure), 22. The Hatch-Waxman Act reflects a carefully crafted framework that balances the interests of innovator and generic drug companies. *Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1370-71 (Fed. Cir. 2002). As part of that balanced framework, Congress established that district court litigations involving paragraph IV challenges ordinarily should be resolved within 30 months while regulatory approval of Petitioner’s proposed drug product is stayed. The Board should decline Petitioner’s invitation to upset that Congressional framework because the Petition makes the exact same obviousness challenge as that raised in the ongoing parallel Hatch-Waxman litigation.

Second, the same or substantially similar arguments have been rejected in an earlier Hatch-Waxman case involving a related patent (U.S. Patent No. 11,298,349 (the “’349 patent”), Ex. 1046) with claims substantially similar to the claims in the challenged ’039 patent. That case, the “MSN litigation,” was brought against a generic challenger and went to trial in October 2023. *See Exelixis, Inc. v. MSN Labs. Private Ltd.*, No. 22-228-RGA (D. Del.). The MSN litigation was a 32-

month litigation, involving tens of thousands of documents, hundreds of pages of expert reports, and multiple days of live testimony at trial. *See* Ex. 2001, 1:12; Ex. 2004, 1:12. The district court judge considered and rejected nearly the same argument presented in the Petition. That case is currently on appeal to the Federal Circuit. There is no reason for the Board to invest resources in reviewing the '039 patent in view of the prior proceeding and pending appeal. Indeed, Petitioner repeatedly draws on the trial record of the MSN litigation, including the testimony of Exelixis' experts in that litigation, without acknowledging the relevant context of that evidence or mentioning that the district court found the asserted claim not invalid in the face of similar obviousness challenges.

Third, Petitioner's unpatentability grounds cobble together general references from patents and printed publications and attempt to fill critical gaps in those references with the testimony of two experts, who themselves rely on Exelixis' experts' testimony from the MSN litigation. These hindsight-driven arguments, extending well beyond what the references themselves teach, are not the type of challenge to which the Board should devote its time and resources.

Finally, substantially the same art and arguments already have been considered by the Patent Office in allowing the challenged claims and related

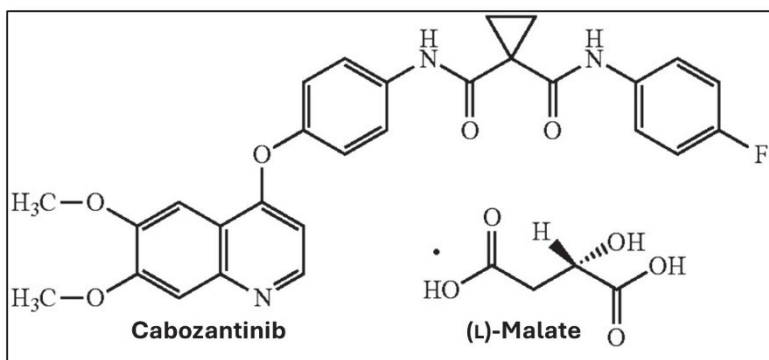
patents. Accordingly, institution would run counter to the judicial economy considerations recognized by 35 U.S.C. § 325(d).

Essentially, Petitioner seeks to collaterally attack what the courts and the Office already have decided in Exelixis' favor after the investment of substantial resources, while also circumventing the current district court case involving the same parties. Accordingly, the Board should deny institution, especially in light of the overall weakness of Petitioner's unpatentability grounds and the reliance on expert testimony rather than patents and printed publications.

II. BACKGROUND

A. Cabozantinib (L)-Malate

Cabozantinib (L)-malate is the active pharmaceutical ingredient ("API") in Exelixis' approved CABOMETYX[®] and COMETRIQ[®] cancer drug products. Ex. 1005, 28; Ex. 1006, 14.



Cabozantinib is Compound IA in the '039 patent. Cabozantinib (L)-malate is Compound IB in the '039 patent and Compound (I) in Brown (Ex. 1003).

B. The '039 Patent

Exelixis faced significant challenges to make cabozantinib (L)-malate API in sufficient scale and purity for formulation into a safe, stable pharmaceutical composition suitable for human administration. *See, e.g.*, Ex. 1001, 3:19-34.

Exelixis' initial synthetic routes included one described in Brown. Ex. 1013, ¶46; Ex. 1026, 45 (¶5).

Exelixis discovered those initial synthetic routes produced API with elevated levels of impurities and degradation products, including 6,7-dimethoxyquinoline-4-ol,¹ which Exelixis discovered was genotoxic. *See* Ex. 1018, 42; Ex. 1013, ¶¶47-48, 50. Exelixis determined “it was critical to essentially eliminate the impurity from the ultimate drug formulation” by ensuring “the lowest levels possible [of 6,7-dimethoxy-quinoline-4-ol] in the API.” Ex. 1013, ¶52; Ex. 2002, 605:19-24.

To achieve the lowest possible levels of 6,7-dimethoxy-quinoline-4-ol, Exelixis developed a new synthetic process, exemplified in the '039 patent. *See*

¹ 6,7-dimethoxyquinoline-4-ol has been referred to as the “1-1 impurity” or just “1-1.” Ex. 1026 (Trial Opinion), n.4.

Ex. 1001, Figure 1; Ex. 1013, ¶¶53-54. Notably, contrary to the allegations of the prior district court defendant, MSN, and Petitioner, there was no easy or predictable fix to the 6,7-dimethoxy-quinoline-4-ol formation problem (which itself was not identified in the prior art), like adding a purification step or swapping out a single reaction sequence. *See* Ex. 2002, 693:14-17, 694:13-695:6 (discussing numerous process changes Exelixis tried for reducing 6,7-dimethoxy-quinoline-4-ol). Indeed, Exelixis spent eight years making significant process changes to develop its new synthetic process described in the '039 patent, which “performs different steps, involves different molecules, and results in different chemistries.” Ex. 1013, ¶54 (citing Ex. 2002, 673:1-674:25); Ex. 1018, 43; Ex. 2002, 358:10-16, 601:21-602:15, 693:14-17, 694:13-695:6.

With these process changes, Exelixis was able to consistently produce a cabozantinib (L)-malate composition comprising 100 ppm or less of impurities, including 6,7-dimethoxy-quinoline-4-ol, using a variety of excipients and formulation methods, and even upon exposure to heat and humidity. *See* Ex. 1013, ¶57; Ex. 2012, 231-232; Ex. 1018, 43-44.

The '039 patent describes and claims Exelixis' invention of a cabozantinib (L)-malate composition essentially free of impurities, including 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

III. THE BOARD SHOULD EXERCISE ITS DISCRETION TO DENY INSTITUTION OF THE PETITION

Under the procedure provided in the Acting Director's March 26, 2025, Memorandum Regarding Interim Processes for PTAB Workload Management ("Memorandum"), parties are permitted to address all relevant considerations that may impact discretionary denial. In addition to the discretionary considerations enumerated in existing Board precedent (e.g., *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020) (precedential)) and the Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019), the Memorandum listed relevant, non-exclusive exemplary discretionary considerations. Here, the prior and concurrent adjudication of closely-related issues in Hatch-Waxman litigation; the extent of the Petition's reliance on expert testimony; the weakness of the unpatentability challenge; and the consideration of closely-related issues by the Office during examination of the '039 patent and its family members all favor denying institution. Petitioner's challenge collaterally attacks prior proceedings in which

the courts and the Office have invested substantial resources and decided in Exelixis' favor, while also sidestepping the current district court case involving the same parties.

A. The Board Should Not Spend Its Limited Resources on the Petition in Light of Ongoing Hatch-Waxman Litigation

Institution should be denied in view of the statutory framework provided by the Hatch-Waxman Act to efficiently and completely resolve infringement and invalidity challenges and promote entry of generic versions of drugs promptly upon expiration of patent claims that are valid and infringed. The Hatch-Waxman Act intended disputes like this one to be resolved in district court litigation within a statutory 30-month timeframe. *See* 21 U.S.C. § 355. Here, Petitioner's challenge of the '039 patent would run in parallel with district court litigation involving identical obviousness challenges. The parallel district court litigation will also include other issues that cannot be decided in an IPR, as well as other unrelated patents involving entirely separate questions requiring resolution before expiration of the 30-month stay, regardless of whether this IPR is instituted. *See* Ex. 2018, 1-2, (Annexure) 22-30; Ex. 2016, 9-18; Ex. 2017, 9-18. In addition, Petitioner's grounds rely on substantially the same art and arguments that were already considered, and rejected, by the district court in the MSN litigation that is now

pending on appeal. Accordingly, institution here would not foster judicial economy or be an efficient use of the Board's limited resources.

1. The Hatch-Waxman Framework Was Carefully Designed to Adjudicate Such Challenges

The Board should deny institution in favor of the forum and procedure Congress specifically established in the Hatch-Waxman Act for handling cases involving generic pharmaceutical patent challenges. *See* 21 U.S.C. § 355. That framework struck a careful balance between incentivizing innovation of new pharmaceuticals while providing generics an expedient pathway to challenge patents and obtain regulatory approval upon successful challenge or upon expiration of patents determined to be valid and infringed. *See FTC v. Actavis, Inc.*, 570 U.S. 136, 141-44 (2013). Under that statutory framework, the proper forum for adjudication of these invalidity challenges is in district court, where Exelixis filed a complaint against Petitioner within 45 days of receiving notice of Petitioner's paragraph IV certification based on its filing of a New Drug Application under § 505(b)(2) of the Food, Drug, and Cosmetics Act, codified at 21 U.S.C. § 355(b)(2), seeking approval to market a version of CABOMETYX[®] before expiration of the '039 patent and several other Orange Book-listed patents—thus triggering the statutory 30-month stay. *See Exelixis, Inc. v. Azurity*

Pharms., Inc., No. 25-478-RGA (D. Del.); Ex. 2016 (Azurity Complaint), 8-20; Ex. 2017 (Azurity First Amended Complaint), 8-20; 21 U.S.C. § 355(c)(3)(C), (D).

The Hatch-Waxman Act contemplates litigation where an application is filed seeking FDA approval to market a version of an FDA-approved drug before expiration of a listed patent. *See* § 355(c)(3)(C), (D). The application must certify for any patents claiming the drug (or its approved use) that (i) the patent information has not been listed with FDA’s Orange Book; (ii) the patent has expired; (iii) the date the patent will expire; or (iv) the patent is either invalid or will not be infringed. § 355(b)(2)(A). Filing an application with paragraph IV certification—which must “include a detailed statement of the factual and legal basis of the opinion ... that the patent is invalid or will not be infringed,” § 355(b)(3)(D)(ii)—constitutes an act of patent infringement under 35 U.S.C. § 271(e)(2), and the patentee can file suit. Filing suit within 45 days of receiving notice of the paragraph IV certification triggers a 30-month stay of approval of the application by the FDA, allowing the courts to address issues of validity and infringement before the proposed product enters the market. As the Supreme Court and the Federal Circuit have explained, the framework provides incentives for both innovators and generics to work expeditiously to meet the 30-month goal.

Actavis, 570 U.S. at 141-44 (describing statutory framework); *Andrx Pharms.*, 276 F.3d at 1370-71 (“Under the [Hatch-Waxman Act], Congress struck a balance between two competing policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market.”); *Actavis Labs. FL, Inc. v. United States*, 131 F.4th 1345, 1356 (Fed. Cir. 2025) (noting “‘careful statutory balance [embodied in the Hatch-Waxman Act] of improving access to lower-cost generic drugs while respecting intellectual property rights’” (brackets in original)). The Board previously has denied institution in light of parallel Hatch-Waxman litigation to avoid duplicative proceedings. *See Mylan Labs. Ltd. v. Janssen Pharmaceutica NV*, IPR2020-00440, Paper 17 at 12-25 (P.T.A.B. Sept. 16, 2020) (denying institution in part because the 30-month statutory stay rendered a stay of the district court case unlikely).

a. Institution Would Upset the Careful Balance Established by Congress

The principles that have led the Board to deny institution in view of co-pending Hatch-Waxman litigation apply with even more force here. First, the Petition raises the exact same obviousness challenge that is identified in Petitioner’s paragraph IV notice letter—indeed, Petitioner “incorporates by

reference the bases for invalidity as set forth in [the] petition[.]” Ex. 2018 (Annexure), 22. Allowing Petitioner to pursue the same validity challenge in multiple venues upsets the carefully crafted framework established by Congress with the Hatch-Waxman Act. Among other things, allowing this IPR to proceed in parallel with the statutorily prescribed district court litigation would foster inefficiency, waste judicial resources, risk inconsistent outcomes, and result in increased uncertainty, burden, and expense to Exelixis, forcing it to defend itself against similar, if not identical challenges, in multiple venues simultaneously. *See* Carlos A. Garcia & Jonathan Stroud, *Ships in the Night*, 68 Am. U. L. Rev. 1111, 1170 (2019) (“Parallel proceedings like [IPRs] were not contemplated when the Hatch-Waxman Act was passed, do not embody the purposes of the AIA itself, and are not an efficient means of litigating disputes like these that are already cabined and complicated by another set of long-implemented statutory schemes. Instead, they harass the patent owner, increase the litigation costs for all parties, and deter settlements with early aNDA filers.”).

As of the filing of this brief, Petitioner has not provided any stipulation asserting that if this IPR is instituted, it would not pursue the grounds in the Petition in district court. Further, as discussed below, Petitioner has in any event

made invalidity arguments beyond those identified in the present Petition. Ex. 2018 (Annexure), 22, 28-29.

The district court is better situated to resolve the full set of issues that will arise in the course of the parties' dispute relating to Petitioner's proposed version of CABOMETYX[®] within the statutory 30-month period. Such issues include non-prior art challenges to the '039 patent that cannot be resolved in an IPR, as well as non-infringement and invalidity challenges to other patents that also cover CABOMETYX[®], which have been raised in Petitioner's paragraph IV notice letter and asserted by Exelixis against Petitioner in the same complaint. Ex. 2018, 1-2, (Annexure) 22-30; Ex. 2016 (Azurity Complaint), 9-18; Ex. 2017 (Azurity First Amended Complaint), 9-18.

Moreover, Petitioner engages in gamesmanship by taking contradictory positions regarding written description in different forums and proceedings. In a separate petition challenging the related '349 patent, Petitioner challenged the written description support for the '349 patent claims in its priority applications. *See Azurity Pharms., Inc. v. Exelixis, Inc.*, IPR2025-00210, Paper 2 at 11-30 (P.T.A.B. Nov. 18, 2024). Notably, the present Petition includes no similar priority challenge—which, if accepted, would render the Petition untimely—even

though Petitioner raised similar written description (and enablement) arguments regarding the '039 patent claims as it did for the '349 patent claims in its paragraph IV notice letter. *See* 35 U.S.C. § 311(c)(1); Ex. 2018 (Annexure), 22-30. Instead, Petitioner filed the present Petition certifying that the '039 patent was available for IPR as of January 9, 2025.

Thus, Petitioner has created “a substantial and unnecessary burden on the Board and [Exelixis][,]... rais[ing] fairness, timing, and efficiency concerns.” Consolidated Trial Practice Guide, 59. While Petitioner (but not, at the time, Exelixis or the Board) knew it would likely be sued due to its anticipated paragraph IV certification and the statutory Hatch-Waxman framework, Petitioner nonetheless filed both petitions in an attempt to sidestep the district court proceedings against it.

2. The Same or Similar Arguments Were Litigated and Rejected by the District Court in the MSN Litigation

Petitioner's challenge of the '039 patent claims repackages several of the arguments that failed in the MSN litigation involving the related '349 patent. Petitioner concedes “the similarity in claim language” between the '349 and '039 patents, both of which claim cabozantinib (L)-malate compositions having low levels of 6,7-dimethoxy-quinoline-4-ol (200 ppm or less in previously tried '349

patent claim 3; 100 ppm or less in the challenged claims of the '039 patent).

Pet. 12. In the MSN litigation, the district court considered, and rejected, arguments that (1) “the Brown process inherently results in a cabozantinib (L)-malate” having 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol, Ex. 1026, 48-51; (2) it would have been obvious to modify Brown to achieve a purity limitation of 200 ppm 6,7-dimethoxy-quinoline-4-ol in a cabozantinib (L)-malate formulation, Ex. 1026, 51-56; and (3) based on generic regulatory guidance, a POSA would have been motivated to use purification techniques disclosed in Robinson to achieve the purity limitation, Ex. 1026, 51-56. Petitioner now reargues these three positions that the district court already considered and rejected. Petitioner relies on the MSN litigation record for fundamental aspects of both of its asserted unpatentability grounds, while futilely trying to patch holes in the theories that were exposed in the MSN litigation.

a. Ground I

For Ground I, Petitioner argues inherency of the purity limitation in Brown’s synthesis, modified by Kubo. Petitioner argues that Ground I is purportedly different because MSN had argued inherency based on Brown alone. Pet. 62-63. But Petitioner does not point to anything in Brown or Kubo that demonstrates what

the actual purity level of 6,7-dimethoxy-quinoline-4-ol would be from the proposed combination. Since Kubo never mentions cabozantinib (L)-malate or 6,7-dimethoxy-quinoline-4-ol, the addition of Kubo does not address a fundamental flaw in the Brown-only inherency theory—namely, the failure to establish that Brown’s synthesis necessarily results in 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol (let alone 100 ppm or less of this impurity, as the present claim requires).

Rather than attempting to quantify how much 6,7-dimethoxy-quinoline-4-ol would result from Brown or its proposed Brown-Kubo combination, Petitioner distorts testimony from Exelixis’ experts in the MSN litigation to argue that “Brown’s cabozantinib (L)-malate was *found to* contain ‘at most, de minimis’ 6,7-dimethoxy-quinoline-4-ol.” Pet. 24. Petitioner purports to support this conclusion with the same testimony that the district court pointed to in rejecting the assertion that claim 3 of the ’349 patent was invalid over Brown. Importantly, the district court testimony was *not* that Brown’s cabozantinib (L)-malate actually *contained* de minimis 6,7-dimethoxy-quinoline-4-ol, but rather that a POSA would have *expected* de minimis 6,7-dimethoxy-quinoline-4-ol to be present at the end of Brown’s synthetic process and, as a result, would not have been motivated to

control for it in the synthetic process or in the final pharmaceutical formulation.

Ex. 1026, 46 (¶10) (“A POSA would not be motivated to minimize the 1-1 impurity after the Brown process because a POSA *would expect* that there is, at most, de minimis impurity left at the end of the Brown process.”) (emphasis added); *see also, e.g.*, Ex. 2002, 669:3-14; Ex. 2003, 709:9-14. The district court considered this same testimony and found that “what a POSA would have expected is not sufficient to show inherency, given that Exelixis presented evidence that the 1-1 impurity did form as a degradation product during the Brown process.” Ex. 1026, 50-51. Petitioner never acknowledges this finding, let alone disputes it. *See* Pet. 45-46.

Petitioner also fails to explain how testimony in the MSN litigation relating to a 200 ppm purity limitation in a claim that was found not invalid could support the invalidity of the claims at issue here, which have even more stringent purity limitations at or below **100 ppm**. Petitioner suggests those lower levels necessarily would have been achieved by modifying Brown’s synthesis with Kubo, without identifying the amount of 6,7-dimethoxy-quinoline-4-ol that allegedly would have formed according to their general combination (as no such data exists).

It is not an efficient use of the Board's resources to revisit the lengthy district court record to determine how the expert testimony about Brown alone might have applied to Petitioner's proposed combination with Kubo against the '039 patent claims, with their more stringent purity limitations.

b. Ground II

For Ground II, Petitioner repeats the argument made in the MSN litigation that generic regulatory guidance, including as described in Robinson, would have motivated a POSA to test for impurities, identify 6,7-dimethoxy-quinoline-4-ol, determine 6,7-dimethoxy-quinoline-4-ol is genotoxic, and, as a result of those tests, control 6,7-dimethoxy-quinoline-4-ol in pharmaceutical compositions made from Brown's API. Ex. 2001, 264:17-266:19, 301:11-303:23 (Dr. Salvatore Lepore); Ex. 2002, 383:19-384:21 (Dr. Maureen Donovan). Petitioner's theory is very similar to the theory rejected by the district court. In the MSN litigation, the district court rejected an obviousness theory that the claimed purity level could be achieved using recrystallization as set forth in Robinson. Here, Petitioner makes the same argument but relies on a different purification technique from Robinson—chromatography rather than recrystallization—but fails to explain why the result would be any different or more predictable than for recrystallization, and

merely speculates via expert testimony, without support from any Petitioner-cited reference, as to purity levels that would be achieved. *See* Pet. 56-57.

Again, although Petitioner relies on a strikingly similar theory to what was tried in the MSN litigation, Petitioner does not address the findings from the district court that defeat its theory. Critically, the court found that a POSA would not have been motivated to control for 6,7-dimethoxy-quinoline-4-ol even considering the regulatory guidance on which Petitioner seeks to rely. *See* Ex. 1026, 45 (¶4), 46 (¶14). As with Ground I, it is not an efficient use of the Board's limited resources to wade through the MSN litigation trial record to review and revisit the district court's analysis.

3. The Petition Relies Heavily on Expert Testimony to Fill Substantial Gaps in the Cited Patents and Printed Publications

Unlike district court litigation, IPRs are statutorily limited to unpatentability grounds based on patents and printed publications. 35 U.S.C. § 311(b). The Board should deny this Petition at least because both grounds extensively rely on expert testimony for essential elements not taught in patents and printed publications, in contravention of Congress's intended limitation on the scope of IPR unpatentability grounds. Indeed, the Acting Director's March 26, 2025, Memorandum specifically identifies the extent of reliance on expert testimony as a

relevant consideration in assessing discretionary denial. As the Patent Office explained in its April 25, 2025, *FAQs for Interim Processes for PTAB Workload Management*, “[w]hile the Board may consider expert testimony, ... extensive reliance on expert testimony ... may suggest that the questions are better resolved in an Article III court. The statute and our reviewing court require that petitions be based on prior art patents and printed publications.”²

Petitioner relies on two separate experts, Dr. Graham Buckton (Ex. 1042) and Dr. William Dichtel (Ex. 1043), to attempt to fill gaps in the patents and publications that nominally form the basis of the IPR. For example, the patents and publications themselves do not suggest how or why the asserted combinations would have supposedly yielded cabozantinib (L)-malate compositions with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

² USPTO, *FAQs for Interim Processes for PTAB Workload Management*, at FAQ 21 (Apr. 25, 2025), https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management?utm_campaign=subscriptioncenter&utm_content=&utm_medium=email&utm_name=&utm_source=govdelivery&utm_term=.

For Ground I, nothing in Brown or Kubo provides any basis for determining the level of 6,7-dimethoxy-quinoline-4-ol resulting from Brown's synthesis, let alone a purported Brown-Kubo synthesis. Indeed, Brown does not even mention 6,7-dimethoxy-quinoline-4-ol would be an impurity or degradation product; Kubo does not mention cabozantinib (L)-malate, let alone 6,7-dimethoxy-quinoline-4-ol. Petitioner's argument that 100 ppm or less necessarily would have been achieved (i.e., that it would have been inherent in this hypothetical combination) is based entirely on expert testimony, rather than anything in the patents or printed publications themselves. Pet. 32 ("Kubo's one-step approach combined with Brown must have necessarily afforded cabozantinib (L)-malate containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol[.]" (citing Dr. Dichtel's declaration, and not Brown or Kubo)).

For Ground II, Petitioner argues that, based on generic regulatory guidance, a POSA would have identified 6,7-dimethoxy-quinoline-4-ol as a genotoxic degradation product in the Brown synthesis, despite citing no patent or printed publication that suggests it was either a degradation product or genotoxic. Pet. 50-55. Petitioner then argues that a generic purification technique (chromatography) would have successfully reduced the level of 6,7-dimethoxy-quinoline-4-ol in

Brown's API to 100 ppm or less, despite citing no patent or printed publication that suggests why chromatography (let alone any particular chromatographic method), specifically, would have been selected or expected to be successful for cabozantinib (L)-malate and 6,7-dimethoxy-quinoline-4-ol. Pet. 55-57. Indeed, in analyzing the purity limitation of claim 1, Petitioner cites its experts' declarations *forty-one* separate times (often citing multiple paragraphs in a single citation), as compared to only three citations to Brown and twelve citations to Robinson, the patents and printed publications that nominally provide the basis for Ground II. See Pet. 50-58. And, notably, *none* of those references to Brown or Robinson mentions 6,7-dimethoxy-quinoline-4-ol as a degradation product.

Petitioner also relies on its own expert's mischaracterizations of testimony from Exelixis' experts in the MSN litigation as the sole alleged support for critical points. For example, Petitioner's expert Dr. Dichtel grounds his opinion as to whether the Brown synthesis would achieve 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol on a misleading snippet of Exelixis' experts' testimony that "at most, de minimis" 6,7-dimethoxy-quinoline-4-ol would have been expected. Ex. 1043, 28 (¶54) ("I understand from counsel that experts for Exelixis have admitted, and that the district court in a litigation over the '349 patent, found Brown's

cabozantinib (L)-malate **to contain** ‘at most, de minimis’ 6,7-dimethoxy-quinoline-4-ol. To avoid any confusion, I will adopt the same ‘de minimis’ terminology for the product of Brown’s synthesis.”) (citation omitted, emphasis added).

Furthermore, Dr. Dichtel misrepresents what the trial experts said and what the district court found. As the district court opinion in the MSN litigation makes clear, the testimony at issue related to **expectations**, not to whether the impurity was actually present in material prepared by Brown’s process. The court found, based on the expert testimony, that “MSN has not shown ... that if the Brown process is followed, it will result in a cabozantinib (L)-malate API essentially free of the 1-1 impurity,” due to the unexpected finding that it could “form as a degradation product during the Brown process.” Ex. 1026, 46 (¶¶8-9).

4. The Merits of Petitioner’s Unpatentability Theories Are Weak

Another factor favoring discretionary denial is the weakness of Petitioner’s unpatentability theories. As described above (*supra* Section III.A.2), Petitioner borrows heavily from the MSN litigation, where the district court rejected similar obviousness theories. Also as described above (*supra* Section III.A.3), Petitioner relies on expert testimony (and mischaracterization thereof) rather than patents and printed publications for critical points in its unpatentability theories.

Patent Owner will further address the deficiencies of the Petition's merits in its forthcoming Preliminary Response, but just by way of example, both grounds suffer from fundamental weaknesses. Ground I argues inherency, which is a "high standard." *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014) ("A party must ... meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis[.]"). Yet Petitioner offers no new evidence of achieved levels of 6,7-dimethoxy-quinoline-4-ol based on its prior art combination and ignores evidence of the challenges encountered by Exelixis and its substantial efforts to develop the synthesis disclosed in the '039 patent and achieve the claimed purity levels. *See supra* pp. 5-6.

Ground II argues, essentially, that any purity limitation for any pharmaceutical composition would have been obvious because of generic regulatory guidance that requires identifying and controlling impurities. For example, Petitioner argues that "it is of no moment that Brown does not expressly report [the] presence or absence" of 6,7-dimethoxy-quinoline-4-ol, because "Brown specifically identified cabozantinib (L)-malate for development as a pharmaceutical" and Robinson generally "discusses strategies for complying with

these [regulatory] requirements,” with “examples of the pharmaceutical industry’s compliance.” Pet. 50-51. This theory is generic and could apply to any API and impurity other than cabozantinib (L)-malate and 6,7-dimethoxy-quinoline-4-ol. And again, the Petition offers no new evidence of achieved levels of 6,7-dimethoxy-quinoline-4-ol based on the prior art.

The Board should not devote its limited resources to reviewing the Petition’s fundamentally flawed theories.

B. The Petition Should Be Denied Under 35 U.S.C. § 325(d)

The Board should further exercise its discretion to deny institution because the Petition presents art and arguments substantially the same as those already considered by the Office. Institution therefore would run counter to the judicial economy Section 325(d) is intended to promote.

Advanced Bionics provides for considering “(1) whether the same or substantially the same art ... or ... arguments previously were presented to the Office; and (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims.” Paper 6 at 8. Both prongs favor denial here.

1. *Advanced Bionics* Prong 1: The Office Already Considered the Same or Substantially the Same Art and Arguments

As set forth below, during prosecution of the application that became the '039 patent and its family members, the Office extensively considered (i) Brown, (ii) Brown in view of Kubo, (iii) Brown in view of regulatory guidance substantially similar to Robinson, and (iv) Brown in view of general reference works on pharmaceutical formulation, including in an obviousness context.

In evaluating whether the same or substantially the same art or arguments were presented previously to the Office, the Board considers the following *Becton, Dickinson* (“*BD*”) factors: (a) similarities and material differences between the Petitioner’s art and the art involved during examination; (b) the cumulative nature of the Petitioner’s art and the art evaluated during examination; and (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art. *See Advanced Bionics*, Paper 6 at 9-10; *NHK Spring Co. v. Intri-Plex Techs., Inc.*, IPR2018-00752, Paper 8 at 11-12 (P.T.A.B. Sep. 12, 2018) (precedential) (quoting *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017) (informative)).

BD factors (a), (b), and (d) favor discretionary denial.

a. Ground I

i. The Office Considered Brown in View of Kubo

Ground I alleges obviousness over Brown in view of Kubo. Pet. 11.

Petitioner argues that prong 1 “is largely inapplicable” because, during prosecution of the application that became the ’039 patent, the Office only rejected the claims as anticipated by Brown and for obviousness-type double patenting (“OTDP”), and thereby failed to consider the obviousness of the claims over Brown in combination with Kubo. *See* Pet. 65. But Petitioner overlooks that the Office’s anticipation rejection required the Office to consider whether Brown discloses all elements of the claims. In the rejection, the Examiner argued that “Brown teaches the instant compound salt and treatment of cancer,” Ex. 2013, 140, and Applicant responded that “Brown does not teach a pharmaceutical composition of [cabozantinib (L)-malate] that contains 6,7-dimethoxy-quinoline-4-ol, let alone 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol” and that “Brown does not disclose any level of purity in the pharmaceutical composition of [cabozantinib (L)-malate].” Ex. 2013, 126. The Examiner subsequently agreed that “[Brown] does not have the ‘less than 100ppm’ in the claims or specification,” and therefore “[the 102 rejection] will be removed.” Ex. 2013, 118. Petitioner does not allege that Kubo alone discloses this limitation, instead arguing that such would necessarily

result from modifying the Brown process with Kubo. *See* Pet. 32-34. Given that both Brown and Kubo are silent as to the 100 ppm or less purity limitation, the Office’s prior consideration of whether Brown discloses that limitation is directly relevant to the core of Petitioner’s challenge.

Petitioner also overlooks that Defendant MSN’s Opening Post-Trial Brief on Invalidity (“MSN’s Post-Trial Brief”) (Ex. 2014) from the MSN litigation was considered during examination of the ’039 patent. *See* Ex. 2013, 71 (Information Disclosure Statement (“IDS”) citing MSN’s Post-Trial Brief, considered by the Examiner on Jul. 26, 2024). MSN’s Post-Trial Brief, which argues, *inter alia*, that claim 3 of the ’349 patent would have been obvious, substantially overlaps with each of Petitioner’s main positions. For example, MSN’s Post-Trial Brief argues that Brown inherently produced cabozantinib (L)-malate essentially free (containing 200 ppm or less) of 6,7-dimethoxyquinoline-4-ol, or at the least a POSA would have expected “de minimis” 6,7-dimethoxy-quinoline-4-ol at the end of Brown’s process. *See* Ex. 2014, 20-26 (citing testimony from Exelixis’ expert, Dr. David MacMillan); *accord* Pet. 5, 24-25, 30-31, 47, 50; *supra* Section III.A.2.a. Here again, the Office considered whether Brown discloses a specific

purity limitation which, as discussed above, is directly relevant to the core of Petitioner's challenge.

Additionally, Petitioner's focus on what was considered during prosecution of the '039 patent takes a narrow view of what was "previously presented to the Office" that does not comport with the *Advanced Bionics* and *BD* frameworks. For example, *Advanced Bionics* indicates that the *BD* factors "should be read broadly ... to apply to any situation in which a petition relies on the same or substantially the same art or arguments previously presented to the Office ... during *any* proceeding" pertaining to the challenged patent, such as rejection of the claims in an earlier, related family member. *Advanced Bionics*, Paper 6 at 10 (emphasis in original). Petitioner ignores the full prosecution history of the proceedings in the '039 patent family, during which the Office considered Brown in view of Kubo in its obviousness rejection of the claims in an earlier family member, citing the same disclosure and making very similar arguments as the Petition. Specifically, during prosecution of the application that became U.S. Patent No. 10,123,999 (the "'999 Patent"), an ancestor of the '039 patent, the Office rejected claims directed to a process of preparing cabozantinib and pharmaceutically acceptable salts thereof as obvious over Brown in view of Kubo. Ex. 2008, 760-763. Like Petitioner, the

Office argued that the only difference between Brown and the '039 patent process is that Brown does not disclose the one-step conversion of the chloroquinoline to the aniline intermediate. *See id.*, 761; Pet. 25, 32. The rejection stated that “Kubo teaches the process of preparing the amine substituted compound” and it would have been obvious to modify Brown with the one-step procedure in Kubo because “the compounds [in Kubo] are generally of sufficiently close structural similarity” and “possess similar properties” to the compounds in Brown, and a POSA “would have been motivated by the desire in the art to reduce unnecessary steps.”

Ex. 2008, 761-763. The Office combined the same disclosure in Brown and Kubo as Petitioner, with the same argument for motivation to combine, which Applicant ultimately overcame. *Compare id.*, with Pet. 33-34. While the claims prosecuted in the '999 patent were process claims, the Office's consideration of Kubo is applicable to the challenged claims because, as discussed above, prosecution proceedings in earlier, related family members are properly included in the *Advanced Bionics/BD* analysis.

Further, both Brown and Kubo were cited on an IDS considered by the Office during examination of the '039 patent. *See* Ex. 2012, 17, 25. Although Petitioner attempts to discount this, *see* Pet. 65 (citing *Bowtech, Inc. v. MCP IP*,

LLC, IPR2019-00382 Paper 12 at 12 (P.T.A.B. Aug. 6, 2019)), more recent Board decisions have credited references cited on an IDS as “previously presented to the Office” under *Advanced Bionics*, particularly when coupled with other evidence of prior consideration by the Office (e.g., in rejections). *See Weatherford U.S., L.P. v. Enventure Global Tech., Inc.*, IPR2020-01661, Paper 19 at 15-16 (P.T.A.B. Apr. 15, 2021) (“[P]reviously presented art includes art made of record by the Examiner, and art provided by an applicant, such as on an Information Disclosure Statement (IDS), in the prosecution history of the challenged patent.” (citing *Advanced Bionics*, Paper 6 at 7-8.)). Here, the Office not only considered Brown and Kubo from the IDS, but also did so in a related patent’s prosecution history where Brown and Kubo were combined to form an obviousness rejection in a manner similar to how Petitioner attempts to use them here.

ii. The Office Considered “Known” Formulation Techniques

Petitioner further argues that formulating the claimed pharmaceutical composition from cabozantinib (L)-malate satisfying the claimed purity level of 6,7-dimethoxy-quinoline-4-ol (as allegedly provided by Petitioner’s Brown-Kubo combination) would have been obvious over Brown because Brown generically discloses a pharmaceutical composition, and selecting the claimed

pharmaceutically acceptable carrier would have been a matter of “known techniques.” *See* Pet. 34-37. The Office considered this argument, too.

During examination of the application that became the related ’349 patent, the Office rejected the claims as obvious over Brown in view of the following references: (1) Li *et al.*, Lubricants in Pharmaceutical Solid Dosage Form; (2) Pingali *et al.*, Mixing Order of Glidant and Lubricant—Influence on Powder and Tablet Properties; and (3) Overview of Pharmaceutical Excipients Used in Tablets and Capsules. Ex. 2012, 239-241. These references provide general overviews of formulation techniques. The Office, like Petitioner, argued that achieving the claimed composition would be a matter of known/routine formulation techniques because Brown “teach[es] that [cabozantinib (L)-malate] is substantially pure” and “all the claimed elements”—including excipients (c.f. carriers)—“were known.” *Id.* Applicant overcame this rejection after arguing that none of the cited references taught or suggested the claimed purity level, which was unexpectedly afforded by the claimed compositions. *See id.*, 209-211.

Additionally, MSN’s Post-Trial Brief considered by the Examiner during prosecution of the ’039 patent argued that once having cabozantinib (L)-malate essentially free (containing 200 ppm or less) of 6,7-dimethoxy-quinoline-4-ol, a

POSA would have used “routine formulation” techniques to arrive at a composition of cabozantinib (L)-malate also essentially free of 6,7-dimethoxy-quinoline-4-ol. *See* Ex. 2014, 30-31; *accord* Pet. 35. Thus, the Office considered this argument in allowing the challenged claims.

b. Ground II

i. The Office Considered Robinson’s Substance

Ground II alleges obviousness over Brown in view of Robinson. Pet. 11. The Petition alleges that *Advanced Bionics* prong 1 is not applicable because Robinson “was never presented to the Office” and therefore “the Examiner never had a chance to consider the obviousness arguments in Ground 2.” Pet. 65. However, the *Advanced Bionics/BD* framework does not require that the Office considered the same art and arguments, but instead requires only the same *or substantially the same* art and arguments. *See Advanced Bionics*, Paper 6 at 7-8. That is the situation here.

Robinson is a review of regulatory guidelines on control of genotoxic impurities. *See* Ex. 1039, Abstract. Robinson reviews the same FDA guidance, titled “Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches” (Dec. 3, 2008) (“Genotoxic Guidance”; Ex. 1037), *see* Ex. 1039, 947 n.17, that was considered by the Office during prosecution of the

'039 patent. *See* Ex. 2013, 71 (IDS considered by the Examiner and citing the Genotoxic Guidance). Robinson and the Genotoxic Guidance have similar disclosures—both discuss regulatory requirements for acceptable limits of genotoxic impurities in pharmaceuticals and general strategies for compliance therewith. *Compare* Ex. 1039, Abstract, 946-948 (identification and acceptable limits of genotoxic impurities), 950-959 (general methods to control/reduce genotoxic impurities), *with* Ex. 1037, 1-6 (identification and acceptable limits of genotoxic impurities), 2, 6-13 (general methods to control/reduce genotoxic impurities). Indeed, Petitioner cites to Robinson and the Genotoxic Guidance interchangeably. *See* Pet. 51-54.

In sum, Robinson is cumulative of the Genotoxic Guidance that was considered by the Office, which weighs in favor of discretionary denial. *See Becton, Dickinson*, Paper 8 at 21-22.

ii. The Office Considered the Substance of the Petition's Obviousness Argument Over Brown and Robinson

The Office considered whether Brown discloses the claimed purity level of 6,7-dimethoxyquinoline-4-ol and whether a POSA would have been motivated to achieve that level in view of regulatory guidance on control of genotoxic impurities, ultimately answering both questions no in allowing the claims.

As discussed above in Section III.B.1.a.i, during prosecution of the '039 patent, the Office made and then withdrew an anticipation rejection based on a Brown family member, ultimately agreeing with Applicant that Brown does not disclose any level of purity in the composition, let alone 100 ppm or less of 6,7-dimethoxyquinoline-4-ol. Ex. 2013, 118, 126. Notably, the Examiner maintained this conclusion even after considering the substance of Robinson via the Genotoxic Guidance. *See id.*, 118 (Interview Summary, Apr. 18, 2024, agreeing Brown does not disclose the purity limitation), 71-72 (IDS citing the Genotoxic Guidance, Date Considered: Jul. 26, 2024), 19 (Notice of Allowance, Aug. 22, 2024).

Additionally, during prosecution of the related '349 patent, the Office alleged the claims were obvious over Brown's disclosure that cabozantinib (L)-malate is "substantially pure," ultimately allowing the claims in view of Applicant's arguments that this is not the same level of purity as claimed, a level of purity unexpectedly afforded by the claimed compositions. *See* Ex. 2012, 240 (obviousness rejection over Brown), 210 (Applicant's response), 178 (allowance). Here too, the Office was presented with FDA guidance on acceptable impurity levels in drug products, yet still ultimately allowed the claims as non-obvious over Brown. *See id.*, 212 (Applicant's argument that the claimed purity level was far

below that required by FDA's *Guidance for Industry: Q3B(R2) Impurities in New Drug Products* (2006) ("*Q3B Guidance*"), 188 (IDS considered by the Examiner and citing the same); *see also id.*, 225 (inventor declaration stating that the MSDS for 6,7-dimethoxy-quinoline-4-ol indicated it "has acute oral toxicity and is harmful if swallowed").

Furthermore, the Office considered Petitioner's arguments based on Robinson/regulatory guidance on genotoxic impurities when it considered MSN's Post-Trial Brief before allowing the '039 patent. MSN's Post-Trial Brief argued, like Petitioner, that it would have been obvious to arrive at the claimed level of 6,7-dimethoxyquinoline-4-ol by starting with its use as a starting material in Brown, recognizing its structure to be potentially genotoxic, and then following regulatory guidance to minimize it. *See* Ex. 2014, 19, 26-30 (citing testimony from Exelixis' expert, Dr. Allan Myerson); *accord* Pet. 2, 10, 17-21, 35, 48-54.

Moreover, as discussed above in Section III.B.1.a.ii, during prosecution of the related '349 patent, Applicant overcame an obviousness rejection over Brown in view of "known formulation techniques." As discussed above in Section III.B.1.a.ii, a similar obviousness argument against the '349 patent was made in MSN's Post-Trial Brief, which the Office considered before allowing the '039

patent. *See* Ex. 2014, 19, 30-31 (citing testimony from Dr. Myerson); *accord* Pet. 57-58.

For at least the foregoing reasons, *Advanced Bionics* prong 1 favors discretionary denial.

2. *Advanced Bionics* Prong 2: Petitioner Has Not Identified a Material Error by the Office

In evaluating whether Petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims, the Board considers the following *BD* factors: (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments. *See Advanced Bionics*, Paper 6 at 9-10. Analysis of these factors confirms Petitioner has failed to identify any material error and to present any additional evidence or facts that warrant institution.

a. *BD* Factor (c): Asserted Art Was Extensively Evaluated During Examination

As discussed above in Section III.B.1, during prosecution of the application that became the '039 patent and its family members, the Office extensively

considered (i) Brown, (ii) Brown in view of Kubo, (iii) Brown in view of regulatory guidance substantially similar to and summarized by Robinson, which is a review article, and (iv) Brown in view of general reference works on pharmaceutical formulation, including in an obviousness context.

b. *BD* Factor (e): Petitioner Has Not Identified Any Examiner Error

“[W]hen a prior art reference presented in a petition was already considered substantively [during examination], the petitioner has the initial burden to identify such errors made by the examiner with respect to that ... reference.” *Ziegmann v. Stephens*, IPR2015-01860, Paper 13 at 10 (P.T.A.B. Sept. 6, 2017). Material error can include “misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims” or legal error, such as an incorrect claim construction. *Advanced Bionics*, Paper 6 at 8-9 n.9. Here, the Petition merely disagrees with the rejections the Office chose to raise during prosecution of the ’039 patent and fails to consider the rejections the Office raised in earlier family members. This does not establish material error.

First, Petitioner incorrectly contends the Office “plainly erred by relying solely on a theory of anticipation.” Pet. 65-66. As discussed above in Section III.B.1.a, Petitioner ignores that, in rejecting the claims as anticipated by Brown,

the Office considered whether Brown discloses or “necessarily afford[s] the claimed compositions” (*see* Pet. 66), ultimately deciding it did not by withdrawing the rejection. Whether Brown discloses the claimed compositions is relevant to Petitioner’s obviousness challenge. As discussed above in Sections III.B.1.a.i-ii, Petitioner also ignores that the Office rejected the ’039 patent’s ancestors as obvious over Brown in view of Kubo and obvious over Brown in view of general reference works on pharmaceutical formulation, raising the very same arguments as the Petition. *See* Ex. 2008, 761-763; Ex. 2012, 239-242; Pet. 30-47, 57-58.

Second, Petitioner is wrong that the Office erred in failing to consider regulatory guidance on genotoxic impurities and the potential genotoxicity of 6,7-dimethoxy-quinoline-4-ol. *See* Pet. 66, 52-53. The Office considered Petitioner’s arguments when it considered MSN’s Post-Trial Brief during examination of the ’039 patent.

MSN’s Post-Trial Brief argues that a POSA would have been alerted to the potential genotoxicity of 6,7-dimethoxy-quinoline-4-ol by its quinoline structure, and then would have understood from FDA guidance that 6,7-dimethoxy-quinoline-4-ol therefore needed to be reduced to the claimed low ppm levels. *See* Ex. 2014, 27-29. As discussed above in Sections III.B.1.a.ii and III.B.1.b.ii,

MSN's Post-Trial Brief includes arguments against the '349 patent that are also highly similar to Petitioner's arguments regarding Brown and "known" formulation techniques. The Office therefore had Petitioner's core arguments laid out for it in MSN's Post-Trial Brief it considered and did not err just because it reached a different conclusion than Petitioner advocates here.

Furthermore, as discussed above in Section III.B.1.b, the Petition ignores that the Office considered 6,7-dimethoxy-quinoline-4-ol's toxicity and regulatory guidance on impurity limits in pharmaceutical products. Specifically, the Office considered (i) the Genotoxic Guidance, which is cumulative of Robinson; (ii) Applicant's unexpected results that the claimed formulations afford "much lower" levels of impurities than required by the *Q3B Guidance*; and (iii) the inventor declaration's statement that the MSDS for 6,7-dimethoxy-quinoline-4-ol indicated it "has acute oral toxicity and is harmful if swallowed."

c. *BD* Factor (f): No Additional Evidence Warrants Reconsideration

No additional evidence warrants reconsideration of the asserted art or arguments.

Petitioner incorrectly claims that the Office did not have the benefit of Exelixis' expert testimony from the MSN litigation regarding (i) the expectation of

de minimis 6,7-dimethoxy-quinoline-4-ol at the end of Brown; and (ii) the potential genotoxicity of 6,7-dimethoxy-quinoline-4-ol. Pet. 66. As discussed above in Sections III.B.1.a.i and III.B.1.b.ii, the Office considered MSN's Post-Trial Brief from that litigation involving the '349 patent, which discusses the same expert testimony Petitioner claims the Office did not have, to make arguments (albeit unavailing ones) substantially similar to Petitioner's.

Moreover, as discussed above in Section III.A.3, Petitioner mischaracterizes Exelixis' expert testimony and, in any event, their heavy reliance on expert testimony supports discretionary denial. As discussed above in Sections III.A.2 and III.A.4, the overall weakness of the grounds and their similarity to arguments rejected by the district court in the MSN litigation further reinforce that the Petition presents no additional evidence warranting reconsideration of the asserted art or arguments.

For at least the foregoing reasons, both prongs of *Advanced Bionics* and all *BD* factors favor discretionary denial.

IV. CONCLUSION

Based on the foregoing, institution of *inter partes* review should be denied under 35 U.S.C. § 314(a) and/or 35 U.S.C. § 325(d).

/Emily R. Whelan/
Emily R. Whelan (Reg. No. 50,391)

PATENT OWNER'S EXHIBIT LIST

Exhibit No.	Description
2001	Trial Tr. Vol. 1, Oct. 23, 2023, <i>Exelixis, Inc. v. MSN Labs. Private Ltd., et al.</i> , No. 22-228-RGA (D. Del.)
2002	Trial Tr. Vol. 2, Oct. 24, 2023, <i>Exelixis, Inc. v. MSN Labs. Private Ltd., et al.</i> , No. 22-228-RGA (D. Del.)
2003	Trial Tr. Vol. 3, Oct. 25, 2023, <i>Exelixis, Inc. v. MSN Labs. Private Ltd., et al.</i> , No. 22-228-RGA (D. Del.)
2004	Trial Tr. Vol. 4, Oct. 26, 2023, <i>Exelixis, Inc. v. MSN Labs. Private Ltd., et al.</i> , No. 22-228-RGA (D. Del.)
2005	<i>Reserved</i>
2006	<i>Reserved</i>
2007	<i>Reserved</i>
2008	File History (Partial) for U.S. Patent Application No. 15/348,716
2009	<i>Reserved</i>
2010	<i>Reserved</i>
2011	<i>Reserved</i>
2012	File History (Partial) for U.S. Patent Application No. 17/170,275
2013	File History (Partial) for U.S. Patent Application No. 18/436,836
2014	Defendants' Opening Post-Trial Brief on Invalidity, Dec. 12, 2023, <i>Exelixis, Inc. v. MSN Labs. Private Ltd., et al.</i> , No. 22-228-RGA (D. Del.)

Exhibit No.	Description
2015	<i>Reserved</i>
2016	Complaint, <i>Exelixis, Inc. v. Azurity Pharms., Inc. et al.</i> , No. 25-cv-00478 (D. Del. Apr. 18, 2025), D.I. 1
2017	First Amended Complaint, <i>Exelixis, Inc. v. Azurity Pharms., Inc. et al.</i> , No. 25-cv-00478 (D. Del. Apr. 24, 2025), D.I. 7
2018	Letter from Azurity Pharms., Inc. to Exelixis, Inc. Re: Notice of Paragraph IV Certification (Mar. 5, 2025), Letter and Enclosure Annexure C

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Discretionary Denial Brief contains 8,013 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. §42.24(d), excluding the parts exempted from the word count by 37 C.F.R. §42.24(a)(1).

By: /Emily R. Whelan/
Emily R. Whelan (Reg. No. 50,391)

CERTIFICATE OF SERVICE

I hereby certify that on May 5, 2025, I caused a true and correct copy of the following materials:

- Patent Owner's Discretionary Denial Brief
- Word Count Certification Under 37 CFR §42.24(d)
- Patent Owner's Exhibit List
- Exhibits 2001-2004, 2008, 2012-2014, and 2016-2018

to be served via e-mail, as consented to by Petitioner, on the following attorneys of record:

amorrell@windelsmarx.com
akayal@windelsmarx.com
lkuhn@windelsmarx.com
AzurityIPRs@windelsmarx.com

By: /Cindy Kan/

Cindy Kan (Reg. No. 76,385)
Wilmer Cutler Pickering Hale and Dorr LLP
7 World Trade Center
250 Greenwich Street
New York, NY 10007
Tel: 212-295-6470
Email: cindy.kan@wilmerhale.com